REMARKS

Information Disclosure Statement

A Supplemental Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the IDS is respectfully requested.

Interview Summary

Applicants' Agent would like to thank the Examiner for conducting the telephonic interview of January 14, 2004. During the interview, the written description and enablement rejections of record were discussed.

Pending Claims

Claims 172-209 are currently pending in the application. The Office Action of October 29, 2003 indicates that only Claims 172-184, 186 and 188-192 are pending. Correction is respectfully requested.

Claim Amendments

Claim 172 has been amended to recite that an amino acid *becomes* selectively coupled to a functional group, rather than recite that an amino acid *is* selectively coupled to a functional group. No new matter has been added.

Rejection of Claims 172-184, 186 and 188-192 under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 172-184, 186 and 188-192 are rejected under 35 U.S.C. § 112, first paragraph; the Examiner states that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed.

The Examiner states that the specification is directed to the use of photolithographic techniques in methods of making arrays of chemical compounds. The Examiner further states that the use of photolithographic techniques is critical or essential to practice the invention.

Applicants respectfully disagree. The teachings of the specification are in no way limited to the use of photolithographic techniques in making arrays, nor is the use of photolithographic techniques critical or essential to practicing the invention. Indeed, the specification specifically

exemplifies how photolithography can be used as one deprotection method to selectively activate a positionally defined location on a surface. However, in view of the teachings of the specification, it is clear that there are a number of alternative activating methods that can be used with similar effect in the instantly-claimed methods.

The Examiner has relied on *University of California v. Eli Lilly and Co.* in the instant rejection, stating that "this holding would be deemed to be applicable to any compound or methods of making compounds or arrays; which requires a representative sample of methods of making the compounds and/or a showing of sufficient identifying characteristics; to demonstrate possession of the claimed generic(s)". As discussed below, the instant specification discloses sufficient identifying characteristics of several selective activation methods other than photolithography that can be used in the invention.

The only feature of the claimed method that the Examiner has questioned, is the ability one skilled in the art would have had to selectively activate positionally defined locations on the surface of a substrate. Thus, in order to fulfill the standard set by *Eli Lilly*, the specification must set forth sufficient identifying characteristics of the selective activation method.

The working examples involving photolithography demonstrate that the identifying characteristic of selective activation of positionally defined locations on a surface is supplying energy to remove the protecting groups from only the desired area or areas of the surface (i.e., in a directed manner). In the case of photolithography, light serves as the energy source, and a mask is used to define the areas from which the protecting groups are removed. Because the specification teaches that several energy sources are suitable for removing protecting groups (e.g., light, x-ray and electron beams, electric current and chemical agents), it is clear that selective activation of positionally defined locations on a surface can be achieved simply by employing a device or technique analogous to a mask for energy sources other than light. One of ordinary skill in the art would have known what devices or techniques are suitable mask analogues for a particular energy source (e.g., the energy sources listed in the specification), so it was not necessary to provide examples of suitable mask analogues for each energy source. Nevertheless, the specification does describe physically divided or etched substrates having surface features such as trenches, v-grooves and mesa structures (page 26, lines 18-26), which would serve as a mask analogue for chemical agents and, in some embodiments, electric current. There is no need to provide specific examples of forming an array on substrates with these

surface features, because the photolithography examples in the specification are representative of the identifying characteristics that are needed to perform the generic method.

It is noted that one of ordinary skill in the art would have known what protecting groups are suitable for use with a particular energy source and would have known suitable conditions for introducing and removing protecting groups. Examples of protecting groups and methods of using them were well known in the art. Therefore, it was not necessary to provide examples of particular combinations of protecting groups and energy sources and conditions for their use to fulfill the written description requirement because mere naming of the alternate methods allows one to immediately envisage the method.

In summary, it is not necessary to provide working examples for multiple members of a genus when a single species of that genus demonstrates sufficient identifying characteristics that are representative of the genus and there is further description that supports additional methods. For the present claims, the identifying characteristics involve an energy source that can be targeted to one or more positionally defined locations on a surface (as exemplified with photolithography). As of the effective filing date of the application, one of ordinary skill in the art would have known how to target energy sources such as chemical agents, x-ray and electron beams and electric current using a device or technique that serves as a mask analogue (please see the enablement section for a discussion on how these energy sources are used to target a particular area). The disclosure of the instant application then teaches one of ordinary skill in the art how to apply these selective activation techniques to array synthesis. Because photolithography is representative of the other methods with respect to the significant characteristic of supplying energy in a directed manner, and because naming the other methods allows one of skill in the art to immediately envisage these other methods, the photolithography working example in combination with the naming of the other methods demonstrates possession by Applicants. Thus, Claims 172-184, 186 and 188-209 are adequately described by the specification. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 172-184, 186 and 188-192 under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 172-184, 186 and 188-192 are rejected under 35 U.S.C. § 112, first paragraph; the Examiner states that the specification does not enable one skilled in the art to make and use the invention commensurate in scope with the claims.

The Examiner states that the instant claims "briefly recite" a method of synthesizing a polypeptide array, but that the specification does not provide a sufficient enabling disclosure for the use of chemical or thermal or magnetic techniques to remove the protecting groups from the compounds so that an activated region on the surface is formed.

In considering the *in re Wands* (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)) factors, the Examiner has made a number of unsupported assertions about the instant specification. Applicants will respond to each of these assertions individually below.

A. Direction and Guidance

As acknowledged by the Examiner, the specification discloses that photolithography makes it possible to direct light to relatively small and precisely known locations on the substrate. Applicants maintain that the specification also enables one of skill in the art to use a variety of additional techniques to activate (e.g., deprotect) precisely known locations on the substrate.

Lithographic techniques, in general, are clearly enabled by the specification. As explained in Chapter 4 of "VLSI Technology", which was previously submitted as an exhibit, lithography can involve light, x-rays, electron beams and other forms of radiation. It is readily apparent from the specification that the photolithography examples are analogous to the methods that would be used with another lithographic technique. The only requirement is that the mask used be functionally impermeable to the type of radiation being employed.

Techniques other than lithography are also enabled by the specification. In the case of chemical agents, the specification teaches that substrates can be physically divided or etched to result in surface features such as trenches, v-grooves and mesa structures (page 26, lines 18-26). These surface features are able to contain a volume of liquid, so that the liquid only contacts a positionally defined location of a surface (rather than spreading across the surface as a whole). In other words, the surface features confer selectivity upon which areas of a surface are activated.

These surface features allow a positionally defined location to be isolated, so that other energy sources such as a magnetic field, electric current and thermal energy can also be selectively applied to a single region. As of the effective filing date, for example, microelectrodes were known (and are disclosed in the specification), and these microelectrodes could be used to deliver a magnetic field, electric current or thermal energy to a single region of a surface, thereby activating that region.

More broadly, microchips were known and in use (e.g., in personal computers) as of the effective filing date of the instant application. Clearly, the ability to manufacture microchips relies, in part, upon delivering energy to a positionally defined location of a surface, just as in array preparation (see, for example, Chapter 4 of "VLSI Technology"). Moreover, miniature electronics such as microchips that were available as of the effective filing date of the application allow one of skill in the art to apply an electric current to a positionally defined location, which also generates a magnetic field and heat at that positionally defined location.

Thus, as of the effective filing date of the application, one of ordinary skill in the art could have selected from many techniques to deliver energy to a positionally defined location of a surface. Although photolithography is specifically exemplified, features on a surface and commercially available electronics were known as of the effective filing date and both allow an energy source to be targeted to a positionally defined location on a surface. There is no need to provide working examples of delivering energy sources other than light to a positionally defined location on a surface because methods of selectively delivering the other energy sources were well known as of the effective filing date.

B. Working Examples

The specification contains working examples that use photolighography. Other techniques are discussed and one of ordinary skill in the art would have known how to adapt other techniques for use in the claimed method. The Examiner has provided no evidence or reasoning to the contrary. Instead, only conclusory statements have been made.

It is pointed out that working examples are not even necessary, provided that the invention is "disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)" (MPEP § 2164.02).

C. Breadth of Claims

The claims are directed to a specific type of method of preparing polypeptide arrays on a surface, which involves definite, positively recited steps. Applicants are entitled to the full scope of the instant claims because the instant application provides a template for preparing polypeptide arrays by these methods. The particular technique by which a positionally defined location is selectively activated in the instant claims is unimportant, so long as it is indeed

selectively activated. The application discloses numerous ways in which a positionally defined location can be selectively activated. It would be unduly burdensome for Applicants to recite each possible activation technique in the claims, and it would deprive Applicants of coverage for the full breadth of their invention.

D. State of the Prior Art

Applicants have provided evidence that the state of the prior art was such that, given the present disclosure, one of ordinary skill in the art could have made the claimed invention. The evidence is present in the semiconductor and chemical arts. The Examiner has not provided any evidence to counter this evidence and is respectfully requested to provide evidence for the assertions made. According to MPEP § 2164.04, "it is incumbent upon the Patent Office, whenever a rejection on this basis [enablement] is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure" (emphasis original).

As discussed above, deprotection of a positionally defined location of a surface depends primarily upon being able to selectively deliver an energy source (including chemical potential energy) to the positionally defined location of a surface. There were numerous methods of selectively delivering an energy source to a positionally defined location that were known as of the effective filing date of the application (e.g., lithography, surface segregation, microelectronics, etc.).

The Examiner is also reminded that a method does not lack enablement because a technique is "difficult" to perform or labor-intensive. Instead, the standard is whether the experimentation required to perform the method is undue. Even if difficult and/or tedious techniques are required for one to make and use the invention, the Examiner has provided no reasoning or evidence to suggest that undue experimentation is required to perform the claimed method. Specifically, it is pointed out that while photolithography is a particularly efficient method of preparing a polypeptide array (primarily because multiple positionally defined locations are activated simultaneously), the amount of effort required for other methods by no means indicates that undue experimentation is required.

E. Predictability of the Art

The Examiner states that the art is inherently unpredictable because organic synthesis of a peptide array on a substrate involving selective protection or deprotection of compounds is not possible without using other methods (e.g., masking using barriers).

Applicants respectfully disagree with the Examiner's statement. The use of protecting groups in organic synthesis was known for decades prior to the effective filing date of the present invention and evidence has been provided to support the assertions made. As such, the behavior of protecting groups is entirely predictable and their release from a compound depends primarily upon being contacted with an energy source (e.g., a chemical agent, light, heat, electric current, magnetic field) to cause bond scission. Although it is often necessary to modify a technique (e.g., masking) to selectively control the location from which protecting groups are removed, a skilled artisan can predict where this location will be based upon where an energy source contacts the protecting groups. (Lasers and lithographic methods, in general, do not require a mask analogue because they can be focused to a very small area.) The discussion above demonstrates that one of skill in the art would have been able to control where an energy source contacts the surface of a substrate by employing a mask analogue, when necessary. Thus, the organic synthesis of a peptide array on a substrate is predictable because the behavior of protecting groups and the methods of controlling where protecting groups are added and/or removed are both predictable.

The Examiner has also made several statements in the Office Action regarding the limitations of particular synthetic methods not appearing in the claims. Applicants wish to clarify the intent of the remarks made in the Supplemental Reply of April 25, 2003. In these remarks, Applicants demonstrated why several specific techniques were enabled by the specification. It is Applicants' position that there are sufficient methods of preparing a polypeptide array enabled by the specification to constitute a genus. The genus simply recites that the surface of a substrate is selectively activated, because the specification discloses a sufficient number of selective activation methods to enable a genus. For this reason, recitations associated with a particular selective activation method (e.g., a reaction chamber, lithography) are not present in the independent claims.

Applicants have shown that the specification enables one of skill in the art to prepare a polypeptide array by a large number of techniques. These techniques often involve selective attachment or removal of a protecting group. Protecting group chemistry was well known, such

that one of skill in the art would have known how to use such groups. The conditions for attaching and removing protecting groups were also well known and could be controlled to act on protecting groups in only a positionally defined location. The chemistry involved in activating a positionally defined location is no different than standard solution- or solid-phase chemistry; it simply occurs in a controlled area. Thus, in view of the teachings of the instant application and the knowledge that one skilled in the art would have had as of the effective filing date, the instant claims are enabled. Reconsideration and withdrawal of the rejection are respectfully requested.

Double Patenting Rejections

U.S. Patent No. 6,379,895 and U.S. Application No. 08/563,759 (Now U.S. Patent No. 6,506,558)

Applicants will consider the filing of a Terminal Disclaimer to overcome the obviousness-type double patenting rejections as appropriate upon notice of otherwise allowable subject matter in the present application. This will permit Applicants to assess the rejections in view of the claims as ultimately indicated to be allowable, since it is possible that the claims may change during the course of prosecution.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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